CRISTALLINE AND AMORPHOUS FORM OF A TRIAZOLO (4,5-D) PYRIDIMINE COMPOUND

This application is a CON of 10/296,990 Dec. 2, 2002 ABN which is a 371 of PCT/SE01/01239 filed May 31, 2001.

The present invention relates to forms of a chemical compound, in particular to crystalline and amorphous forms, more particularly four crystalline forms and an amorphous form. The invention further relates to processes for the preparation of such forms, to pharmaceutical compositions comprising the compound in crystalline and/or amorphous form and to the therapeutic use of such forms.

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of subsequent manufacture of pharmaceutical formulation comprising the active compound. Chemical stability, solid state stability, and shelf life of the active ingredients are also very important factors. The drug substance, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physicochemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility). Moreover, it is also important to be able to provide drug in a form which is as pure as possible. Amorphous materials may present significant problems in this regard. For example, such materials are typically more difficult to handle and to formulate than crystalline material, provide for unreliable solubility, and are often found to be unstable and chemically impure. The skilled person will appreciate that, if a drug can be readily obtained in a stable crystalline form, the above problems may be solved. Thus, in the manufacture of commercially viable and pharmaceutically acceptable, drug compositions, it is desirable, wherever possible, to provide drug in a substantially crystalline, and stable, form. It is to be noted, however, that this goal is not always achievable. Indeed, typically, it is not possible to predict, from molecular structure alone, what the crystallisation behaviour of a compound will be, and this can usually only be determined empirically.

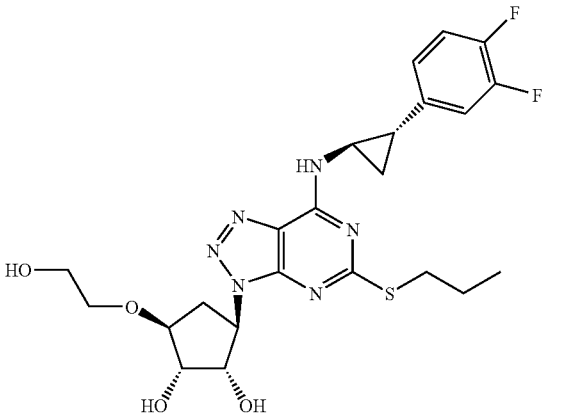
Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these condition, such as thrombolysis and angioplasty are also compromised by platelet-mediated occlusion or re-occlusion.

It has been found that adenosine-5'-diphosphate (ADP) acts as a key mediator of thrombosis. ADP-induced platelet aggregation is mediated by the P_{2T} receptor subtype located on the platelet membrane. The P_{2T} receptor (also known as $P2Y_{ADP}$ or $P2T_{AC}$) is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor which is as yet uncloned. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., *Br. J. Pharmacology* (1994), 113, 1057-1063, and Fagura et al., *Br. J. Pharmacology* (1998) 124, 157-164. Recently it has been shown that antagonists at this receptor offer significant improvements

over other anti-thrombotic agents (see *J. Med. Chem.* (1999) 42, 213). International Patent Application WO 9905143 discloses generically a series of triazolo[4,5-d]pyrimidine compounds having activity as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists. The compound of formula (I) (as depicted below) is embraced by the generic scope of International Patent Application WO 9905143 but is not specifically disclosed therein. This compound exhibits high potency as a P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonist. It also has a surprisingly high metabolic stability and bioavailability.

Accordingly the present invention relates to the compound of formula (I):

(I)



in a substantially crystalline form.

The compound of formula (I) is conventionally named: {1S-[1α, 2α, 3β(1S*,2R*),5β]}-3-(7-{[2-3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-1,2,3-triazolo [4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol.

The compound of formula (I) may exist in four different substantially crystalline forms referred to hereafter as Polymorph I, Polymorph II, Polymorph III and Polymorph IV. A polymorph is a particular crystalline form of a compound.

The different physical properties of polymorphic forms with respect to each other and with respect to the amorphous state may influence markedly the chemical and pharmaceutical processing of a compound, particularly when the compound is prepared or used on an industrial scale.

In one aspect of the invention, the preferred crystalline form of the compound of formula (I) is in the form of Polymorph I, Polymorph II, Polymorph III and/or Polymorph IV.

In an alternative aspect of the invention, a preferred crystalline form of the compound of formula (I) is Polymorph I.

In another aspect of the invention, a preferred crystalline form of the compound of formula (I) is Polymorph II.

In a further aspect of the invention, a preferred crystalline form of the compound of formula (I) is Polymorph III.

In an additional aspect of the invention, a preferred crystalline form of the compound of formula (I) is Polymorph IV.

In a further aspect of the invention, the compound of formula (I) is in a substantially amorphous form. In an amorphous form, the three dimensional long range order that normally exists in a crystalline form (for example in a polymorph) does not exist, and the positions of the mol-